UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/737,544 | 12/18/2000 | Mark B. Pepys | 068800-0275486 | 1521 |

909 7590 03/09/2007

PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

| EXAMINER | |
|---|---|
| WANG, SHENGJUN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/09/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/737,544 | PEPYS, MARK B. | |
| | Examiner | Art Unit | |
| | Shengjun Wang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,10-15,19,49,50,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-15,19,49,50,57,58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTIONA

1. request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 29, 2006 has been entered.

Claimed inventions, the claims as pending are direct to a method comprising administering the compounds in claim 10 to a patient suffering from myocardial infarction or stroke, wherein the method is alleged to treat or prevent CRP-mediated tissue damage. Note "prevent" herein is construed as "to completely stop" and "to keep from happening or existing."

The elected compound hexadecylphosphorycholine is determined to be not obvious over the references on the record, search has been extended

### *Claim Rejections 35 U.S.C. 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 19, 49 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds as defined in claim 10, does not reasonably provide enablement for other compounds "capable of inhibiting the binding of CRP to a ligand. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

3. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ 2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factor to consider when assessing if a disclosure would have required undue experimentation. The court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

The claims are directed to the employment of " a compound capable of inhibiting the binding of CRP to a ligand." The breadth of the claim cover any compounds with the capability Applicant provides examples of those compounds, i.e., those defined in claim 10. The specification provide no further guidance, direction or working examples for any other compounds which may be capable of inhibiting the binding of CRP to a ligand. The art of finding a compound that inhibits the function of a protein, or enzyme is very unpredictable. See University of Rochester v. G.D. Searle &Co. 69 USPQ 2D 1886, wherein the court states "The same is not necessarily true

in the chemical arts more generally. Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, ..."

Applicant uses functional limitation 'compound capable of inhibiting the binding of CRP to a ligand.' to defined the agents employed in the method. A person of ordinary skill in the art would have been required to perform undue experimentation to use claimed invention, particularly, to identify and obtain those 'compound capable of inhibiting the binding of CRP to a ligand.' within claimed scope. Attention is further directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: the vice of a functional claim exists not only when a claims is wholly functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty. Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does little more than outlin[e] goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate□. Applicants functional language at the point of novelty fails to meet the requirements set forth under 35 USC 112, first or second paragraph. Claims employing functional language at the point of novelty, such as Applicants, neither provide those elements required to practice the inventions, nor inform the public during the life of the patent of the limits of the monopoly asserted *General Electric Company v. Wabash Appliance Corporation et* supra, at 468.

The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed of physiological activity. The instant claims read on all compound capable of inhibiting the binding of CRP to a ligand, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention, absent undue experimentation.

4. Claims 1, 10-15, 19, 49, 50 and 57-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating atherosclerosis (see pages 20-37 of the specification herein), does not reasonably provide enablement for preventing atherosclerosis, and for treating and/or preventing of tissue damage in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

5. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ 2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factor to consider when assessing if a disclosure would have required undue experimentation. The court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

The claims are directed to treating and/or preventing tissue damage. "tissue damaging" herein essentially reads on all disorders, including, atherosclerosis, cancers, Alzheimer's disease, viral infections. The state of the art in treating such diseases is low. There is no established method for preventing such disease in the art. It is known it the art that excess amounts of human CRP would induce myocardial infarction, markedly increases morbidity, mortality and the infarct size in animal model (Griselli et al.). Applicant provides evidence showing that, in the same model, CRP inhibitor would suppress the pathogenic effect of CRP. (pages 20-35 herein). But there is no evidence that the method can actually prevent (completely stop) the tissue damage. The specification provide no further guidance, direction or working examples as how the claimed method would be effective in preventing atherosclerosis, no does it provide guidance, direction or working examples for *completely stop* the tissue damage. The art and the instant application have shown that excess amount of CRP may cause tissue damage. However, there is no evidences that CRP is solely response for causing tissue damage. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed of physiological activity. The instant claims read on preventing and/treating preventing and/treating all diseases associated with tissue damage, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention, absent undue experimentation. The court in In re Fisher, 427 F.2d 833, 839; 166 USPQ 18, 24 (CCPA 1970) held that, "in case involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." The more unpredictable an area, the more specific enablement is need in order to satisfy the statue. The Unpredictability is

more apparent where the diseases disclosed in the specification are as complex and diverse in etiology and patient populations as the many types and causes for myocadial infarcation and stroke.

Further, the claims are directed to *preventing tissue* damage in pateitn suffering from myocardial infarction or stroke. Those patients apparently have all the tissue damage. It is not clear how one could prevent a damage that already presents.

***Claim Rejections 35 U.S.C. 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 10, 13-14, 19, 57-58 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Yedgar et al. (US 5,064,817, of record), as evidenced by Bhakdi et al. (IDS) and Kitao.

8. Yedgar et al. teaches that various phosphorylcholine derivatives are known to be useful for treating pathological conditions including atherosclerosis, myocardial infarction. See, particularly, column 13, lines 22-38, and the claims. the effective amounts are about 01 to 100 mg mg/kg/day. See, col. 14, lines 25-33. Bhakdi et al. and Kitao show that phosphorylcholines have the properties for inhibiting the binding of CRP to LDL, See the abstracts. As to the limitation treatment or prevention of C-reactive protein (CRP)-mediated tissue damage," it is noted that the instant claims are directed to effecting a biochemical pathway with an old and well

known compounds. The argument that such claims are not directed to the old and well known ultimate utility (treating myocardial infarction) for the compounds, e.g., phosphorylcholine derivatives, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates.

***Claim Rejections 35 U.S.C.§ 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 10-11, 13-14, 19, 49, 50 and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhakdi et al. (IDS) and Kitao, in further view of Yedgar et al. (US 5,064,817) and Wissner et al. (US 4,640,913).

Bhakdi et al. and Kitao teaches that phosphorylcholine are useful for inhibiting the binding of CRP to LDL, wherein the binding of CRP to LDL is known to be a factor of atherosclerosis. See the abstracts.

The primary references do not teach expressly the employment of phosphorylcholine derivatives for treating patient suffering myocardial infarction or stroke.

However, Yedgar et al. teaches that various phosphorylcholine derivatives are known to be useful for treating pathological conditions including atherosclerosis, myocardial infarction. See, particularly, column 13, lines 22-38, and the claims. Wissner et al. teaches various phosphorylcholine derivatives are useful for treating hypertension, an underline etiology of atherosclerosis, and myocardial infarction. See, particularly, the abstract, column 1, lines 19-26, and the claims.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a phosphorylcholine compound, such as hexadecyl phosphorylcholine, for treating atherosclerosis, hypertension, myocardial infarction, or related disorders, such as stroke.

A person of ordinary skill in the art would have been motivated to employ a phosphorylcholine compound, such as those disclosed by Yedgar et al. and , for treating atherosclerosis because phosphorylcholine is known to inhibiting the binding of CRP to LDL is known to be a factor of atherosclerosis, suggesting the usefulness of phosphorylcholine for treating atherosclerosis, and a ester, or salt of an active therapeutical compound, would have considered, an equivalent of the active therapeutical compound. Further, phosphorylcholine derivatives are generally known to be useful for treating atherosclerosis, hypertension, and myocardial infarction. With respect to stroke, note, a method known to be useful for treating the underline etiology of a disorder would have been reasonably expected to be useful for treating or preventing the disorders.

11. Claims 11, and 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yedgar et al. (US 5,064,817), and Wissner et al. (US 4,640,913), in further view of Bhakdi et al. (IDS) and Kitao.

The teaching by Yedgar et al has been dicussed above. Wissner et al. teaches various phosphorylcholine derivatives are useful for treating hypertension, an underline etiology of atherosclerosis, and myocardial infarction. See, particularly, the abstract, column 1, lines 19-26, and the claims. Note all the phosphorylcholine derivatives disclosed by Yedgar et al. and Wissner et al. read on the general structural defined in claim 10.

Yedgar et al. and Wissner et al. do not teach expressly the treatment of stroke, or the employment of the particular phosphorylcholine.

However, Bhakdi et al. and Kitao teaches that phosphorylcholine are useful for inhibiting the binding of CRP to LDL, wherein the binding of CRP to LDL is known to be a factor of atherosclerosis. See the abstracts.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the claimed invention was made, to use the method of Yedgar et al. and Wissner et al. for treatment of stroke because a method known to be useful for treating the underline etiology of a disorder would have been reasonably expected to be useful for treating or prophylactic treating the disorders. The employment of phosphorylcholine would have been obvious, particularly in view of the teaching by Bhakdi et al. and Kitao, as phosphorylcholine useful for inhibiting the binding of CRP to LDL, wherein the binding of CRP to LDL is known to be a factor of atherosclerosis.

***Response to the Arguments***

12. Applicants' amendments and remarks submitted December 29, 2006 have been fully considered, but are not persuasive.

Regarding the enablement for "preventing", note the claims read on complete stop or keep from happening or existing of tissue damage, which deemed not enabled. The evidences presented in the application or on the record do not enable for preventing.

The amendments fail to distinguish the claimed invention from the prior art on the record. The claims as pending are direct to a method comprising administering the compounds in claim 10 to a patient suffering from myocardial infarction or stroke, wherein the method is alleged to treat or prevent CRP-mediated tissue damage.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The cited references as a whole have fairly suggest the employment of phosphorylcholine derivatives for treatment of patient suffering from myocardial infarction, hypertension, arthrosclerosis because the cited prior art as a whole teaches 1) the compounds are known to be useful for treatment of those diseases, 2) the compounds are known as CRP binding compounds, and 3) CRP binding compounds have been suggested as useful for treatment of those diseases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shengjun Wang
Primary Examiner
Art Unit 1617

SHENGJUN WANG
PRIMARY EXAMINER